REMARKS

The claims have been amended to limit them to the illustrated embodiment of the protein contained in the composition, specifically, the recombinantly produced repeating unit from toxin A of *C. difficile*, formulated to be administered by injection. This is accomplished by inserting the description at page 21, lines 6-10, and limitation of claim 5 into claim 1; thus claims 2 and 4-5 have been canceled as redundant and claims 7 and 8 have been canceled as outside the scope of claim 1. In addition, an inadvertent error in claim 14 has been corrected. Support for a humoral immune response is found, for example, in Example 4 which demonstrates a humoral (antibody) response to the polysaccharide component of the conjugate. No new matter has been added and entry of the amendment is respectfully requested.

Formal Matters

The rejection of claim 14 under 35 U.S.C. § 112, paragraph 2, has been addressed by amendment.

Applicants note the withdrawal of proposed claims 64-66 from consideration; these claims have been permitted to remain pending in this response because applicants believe that should the remaining claims be allowed, these claims, directed to methods to use the compositions claimed, would be rejoined according to standard Office practice.

The Invention

The invention is directed to immunogenic compositions where the immunogen of interest is specifically a polysaccharide and where the polysaccharide is administered with a particularly effective carrier - the repeating unit of the *C. difficile* toxin A (*r*ARU). Applicants have demonstrated the effectiveness of this carrier in the present application, in Example 4 with respect to *Shigella flexneri*, *E. coli*, and *Pneumococcus*. The vaccines are administered by

injection, as set forth in Example 4. See page 21, lines 6-10. This is in contrast to the Thomas document discussed below which describes the adjuvant effects of toxin A (as opposed to *r*ARU) in an administration route which addresses the mucosa directly. With regard to vaccines that are administered by injection, the use of *r*ARU represents employing a larger carrier than those conventionally used with polysaccharide antigens as described in the secondary documents cited by the Office. Thus, the immunogenic compositions claimed are unique in that they are designed for injection, but comprise the particularly effective carrier *r*ARU, the effectiveness of which may be due in part to its larger size than conventional carriers in such vaccines such as keyhole limpet hemocyanin (KLH).

The Rejection Under 35 U.S.C. § 102(e)

Claims 1-8, 12-15, 19-20, 25-26, 28-29, 36-39 and 62-63 were asserted to be anticipated by Thomas, Jr., *et al.*, U.S. patent 5,919,463 (Thomas). First, applicants wish to call the attention of the Office once again to the requirement that the immunogen to which an immune response is to be elicited is a polysaccharide component. Thomas does not even mention polysaccharide components. The section referred to by the Office at column 2, lines 57-67 and column 3, lines 1-8 merely mentions sources of antigens; there is no requirement or suggestion that the antigen be a polysaccharide. Similarly, in the section quoted in column 3, it is clear from the discussion that Thomas envisions antigens which are protein. The relevant portion states that:

> The toxins (referring to the adjuvants) may be recombinant, synthetic, or part of a fusion protein which includes an *H. pylori* urease or polypeptide which facilitates purification of the fusion protein covalently conjugated to an antigen, chemically crosslinked to an antigen, or toxoided.

Again, antigens in general are mentioned, there is no suggestion that the antigen be a polysaccharide. All of the exemplified antigens in Thomas are also proteins or peptides. Accordingly, not only does Thomas not anticipate the invention as claimed (wherein it is required that the antigen be a polysaccharide), Thomas does not even suggest this. Where is there any mention of a polysaccharide antigen in Thomas? There is no such mention.

Similarly, there is no mention in Thomas of the use of *r*ARU as a carrier. *r*ARU is mentioned only as an antigen in Example 5. Only toxin A itself is utilized as an adjuvant.

In short, Thomas mentions neither polysaccharides as antigens nor *r*ARU as a carrier. Thus, each and every element of the claim is not found in Thomas and this basis for rejection may properly be withdrawn.

The Rejections Under 35 U.S.C. § 103

There were a number of rejections under 35 U.S.C. § 103 which combine Thomas with other documents that describe antigens derived from microorganisms specifically named in dependent claims, but not mentioned in Thomas.

As these rejections are made under § 103, a further comment concerning Thomas may be in order. Thomas discloses *C. difficile* adjuvants in the context only of vaccines which are designed for administration to the mucosa. As stated in column 1, lines 34-37, "Thus, *C. difficile* toxins, and fragments thereof, are effective *mucosal* adjuvants which can be used in vaccination methods." Indeed, all of the examples that describe administration of vaccines where *C. difficile* toxin A is the adjuvant use a mucosal route. Examples 1 and 2 describe experiments where the vaccines are administered intranasally. Examples 3 and 4 describe the use of a toxin A fusion protein wherein the repeating unit is coupled to GST not as an adjuvant, but as the antigen to which response is elicited. Example 5, which again uses toxin A as the illustrative adjuvant,

describes vaginal and rectal administration. There is no specific description of injecting compositions where a *C. difficile* derived protein is an adjuvant in Thomas. Thus, the relevant vaccines described in Thomas are not formulated for injection, as required by the claims.

All of the secondary references describe administration by injection. As these routes are independent and impose different demands on the vaccine, there is no incentive to combine the teachings of Thomas with any of the secondary documents.

In addition, none of the secondary documents remedy the failure of Thomas to suggest the invention as now claimed. Thomas fails to suggest, indeed teaches away from, compositions that are formulated for injection; Thomas fails to mention polysaccharides as antigens, and Thomas fails to identify *r*ARU as an adjuvant. With respect to the latter two deficiencies, polysaccharides represent a species of the genus antigens and *r*ARU represents a species of the genus *C. difficile* toxins. There is no specific mention of these species in the appropriate context in Thomas. It is well established that a species not mentioned in the context of a generic invention is patentable thereover. (*In re Jones*, 958 F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); and *In re Baird*, 16 F3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994).) The failure of Thomas to suggest these limitations is not remedied by any of the secondary documents.

Turning now to these documents specifically, the first of these is used as a basis to include claims 23-24 in the rejection (claims 25-26, 28-29, and 62 are not included).

Claims 23-24 require that the pathogenic microorganism is *S. pneumoniae*. As Thomas does not teach *S. pneumoniae*, the Office cites Schneerson, *et al.*, directed to a conjugate vaccine composed of serotype 14 *S. pneumoniae* capsular polysaccharide bound to pertussis toxin. However, there appears to suggestion to combine Schneerson with Thomas in view of the focus of Thomas on only protein antigens, and Thomas is directed to mucosal administration while

Schneerson is directed to injection. As Schneerson is directed to a different type of antigen and type of formulation from that suggested by Thomas, there is no incentive to combine these documents. Even if Thomas is combined with Schneerson, the invention is not suggested as the limitation to *r*ARU as a carrier is not suggested by either document alone or in combination.

The second of these combinations combines Thomas with Taylor, *et al.*; this results in including claims 25-26 which are directed to *Shigella*. Thus, Taylor, *et al.*, is cited as describing polysaccharide conjugates of *Shigella* polysaccharides to bacterial toxoids. Again, as Thomas suggests only enhancing the immune response of peptide or protein antigens, rather than polysaccharides, and Thomas is directed to mucosal administration while Schneerson is directed to injection, there is no motivation to combine these documents. Even if Thomas is combined with Schneerson, the invention is not suggested as the limitation to *r*ARU as a carrier is not suggested by either document alone or in combination.

The third such combination is with Devi, *et al.*; this permits the inclusion of claims 28-29. Claims 28-29 are directed to *N. meningitidis* and *E. coli*, respectively. Again, the secondary document is cited to show polysaccharide antigens from the relevant organisms coupled to a different protein, not from *C. difficile*. This combination is not suggested for similar reasons to that set forth above. Even if Thomas is combined with Schneerson, the invention is not suggested as the limitation to *r*ARU as a carrier is not suggested by either document alone or in combination.

Finally, Thomas is combined with Fattom, *et al.*, and the rejection applied to claims 30-33. The secondary document describes capsular polysaccharides from *S. aureus*, which is included in all of these claims. But the combination is not suggested for the same reasons set forth above. Even if Thomas is combined with Schneerson, the invention is not

suggested as the limitation to *r*ARU as a carrier is not suggested by either document alone or in combination.

Thus, in all cases, the required combination of documents is taught away from by Thomas, in view of Thomas' disclosure directed solely to peptide or protein antigens and focus on mucosal administration. While the secondary documents describe polysaccharide antigens coupled to other proteins, there is no suggestion *r*ARU be substituted for the carrier described in the secondary documents; as Thomas does not suggest *r*ARU either, even the combination does not suggest the invention as claimed.

CONCLUSION

For the reasons set forth above, it is believed that the pending claims, claims 1, 3, 6, 13-15, 19-20, 23-39 and 62-66 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 420522000100.

Respectfully submitted,

Dated: October 15, 2002

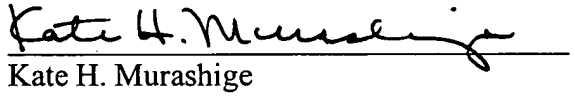
By: 

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

1. (Twice amended) An immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein and a polysaccharide component, wherein said protein [is encoded by a gene from a strain] comprises the toxin A repeating units (*r*ARU) of *Clostridium difficile* and said polysaccharide component is characteristic of a pathogenic microorganism, which pathogenic microorganism is other than *C. difficile*,

wherein said composition is formulated for injection.

14. (Twice amended) The immunogenic composition of claim 1, wherein said immune response comprises [an] a humoral immune response.

64. (Amended) A method to elicit an immune response in a subject to a pathogenic organism which method comprises [administering to] injecting a subject in need of such response with an effective amount of the immunogenic composition of claim 1.

65. (Amended) A method to elicit an immune response in a subject to a pathogenic organism which method comprises [administering to] injecting a subject in need of such response with an effective amount of the immunogenic composition of claim 36.

66. (Amended) A method to elicit an immune response in a subject to a pathogenic organism which method comprises [administering to] injecting a subject in need of such response with an effective amount of the vaccine of claim 37.